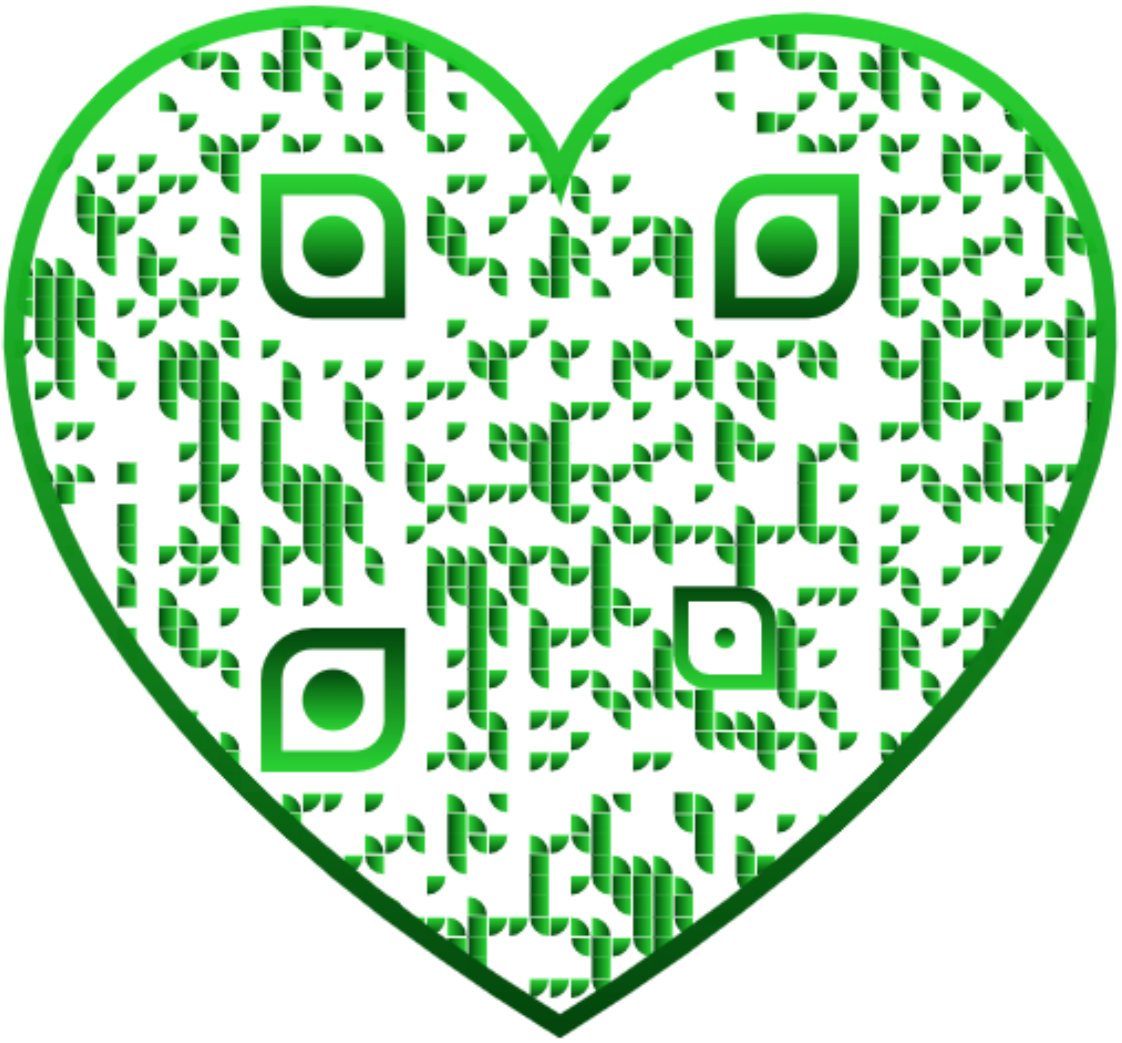
THE DIRTY TRAMADOL

Sadiq Ameen. ABEM



1962

1977

1995

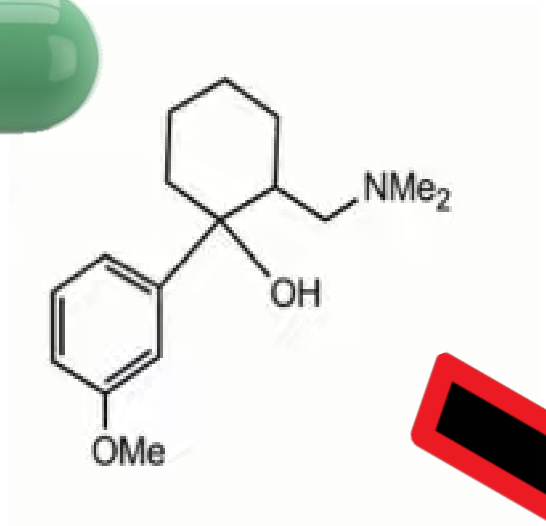
U.S. JUSTICE DEPARTMENT
DRUG ENFORCEMENT ADMINISTRATION

2014

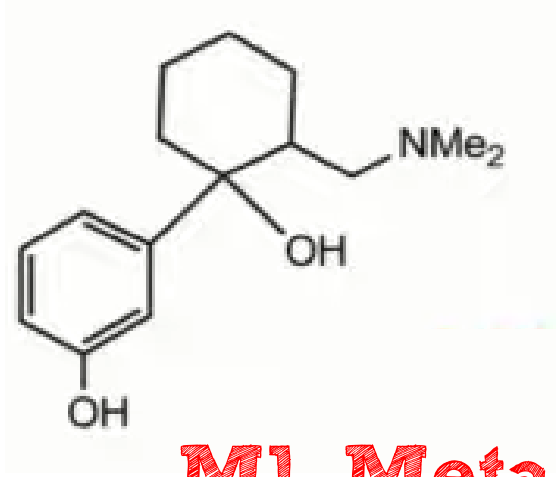
C-IV

Dual Mechanism of Action

Unpredictable kinetics

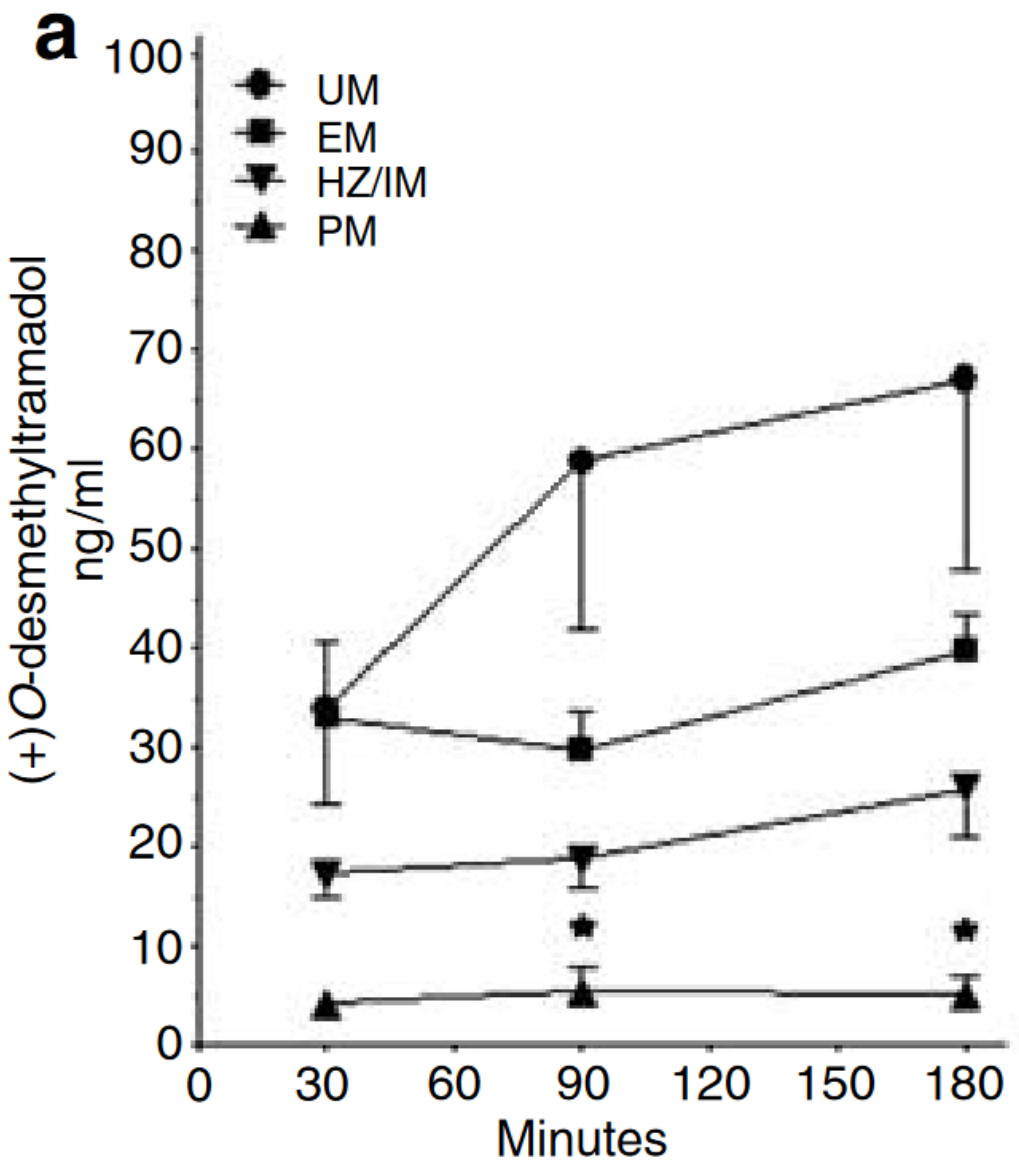


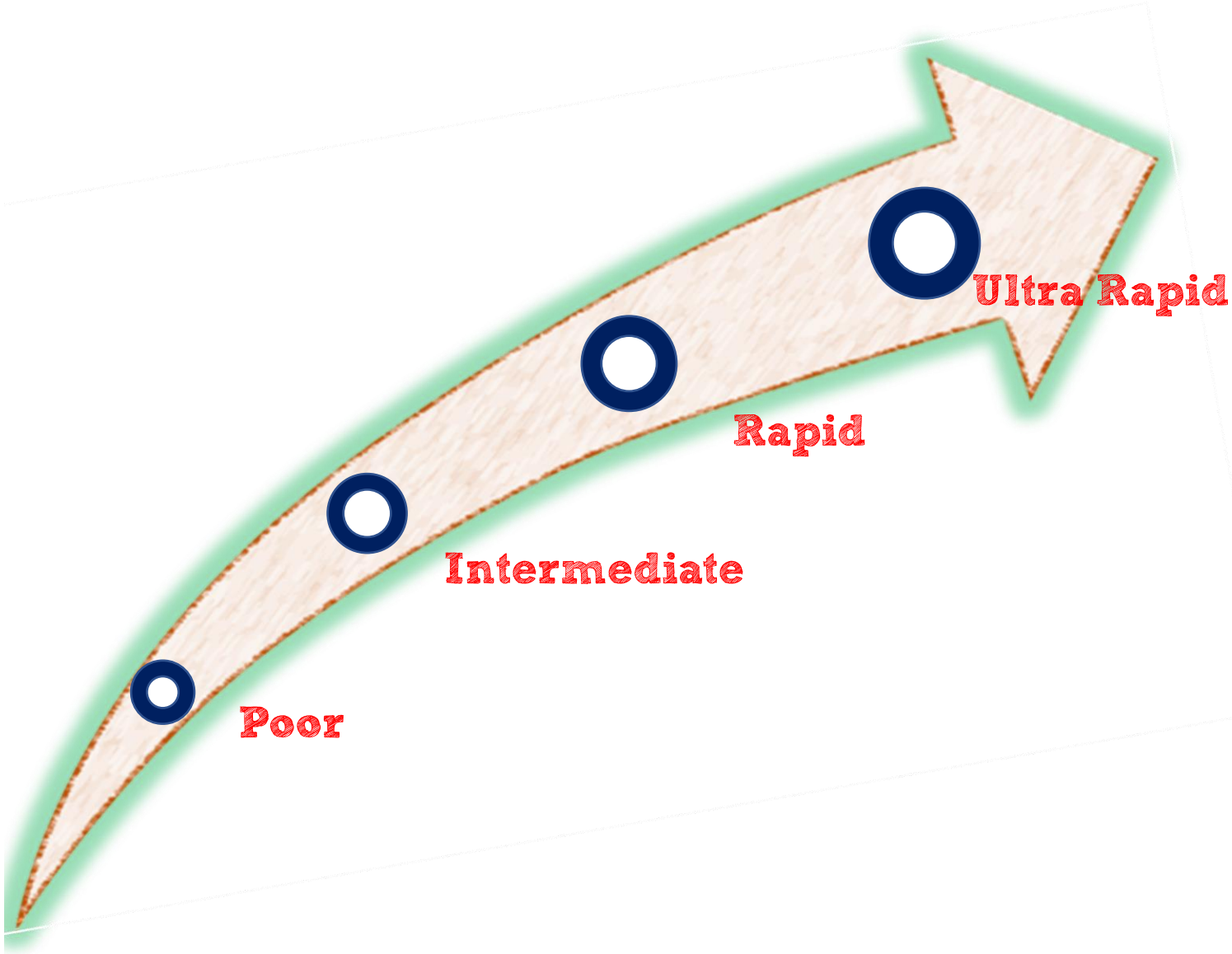
CYP2D6



M1 Metabolite

CYP2D6 Polymorphism





Genetics of CYP2D6

Genetic Type	CYP2D6 Activity	Ethnic Differences (Approximate)
Poor metabolizers	None	Caucasians 6%–10% Mexican Americans 3%–6% African Americans 2%–5% Asians ~1%
Intermediate metabolizers	Low	Not established
Extensive metabolizers	Normal	Most people are extensive metabolizers
Ultrarapid metabolizers	High	Finns and Danes 1% North Americans (white) 4% Greeks 10% Portuguese 10% Saudis 20% Ethiopians 30%

Table I. Impact of CYP2D6 Genetic Variation on Tramadol and Codeine Metabolism.

CYP2D6 Metabolizer Status	Impact on Tramadol and Codeine Metabolism
Ultrarapid Metabolizer (0.7 to 9% of population)	Increased formation of active metabolite (morphine or O-desmethyltramadol) leading to higher risk of toxicity
Normal Metabolizer	Expected active metabolite formation
Intermediate Metabolizer (~30 to 43% of population)	Reduced active metabolite formation
Poor Metabolizer (0.4 to 6% of population)	Greatly reduced active metabolite formation

Tramadol

=

weak Opioid

=

Safe

Efficacy

- **No study that shows Tramadol is superior to NSAIDs!**
- **Single dose Tramadol 100 mg + 400 mg Ibuprofen**
- **Meta-analysis (Prescrine 2003): Tramacet was no more effective than NSAID**
  - **Tramadol/Tramacet superior to T Tylenol but NOT to NSAID**

- **Edwards 2002** (NNT for 50 % pain reduction)

	Dental pain	Post-surgical pain
NSAID	2.3	2.7
Tramadol	9.1	4.4

- **Banerjee 2011:** Tramadol NOT superior to NSAID (Post-operative pain)
- **Prescrine 2003**
  - NOT superior to Percocet (OA, chronic back pain)
  - Tramacet NOT superior to NSAID (dental pain)

European Review for Medical and Pharmacological Sciences 2012; 16: 1983-1988

Tramadol or paracetamol do not effect the diagnostic accuracy of acute abdominal pain with significant pain relief – a prospective, randomized, placebo controlled double blind study

H. OGUZTURK, D. OZGUR[1], M.G. TURTAY, C. KAYAALP[1], S. YILMAZ[1], M. DOGAN[2], E. PAMUKCU[3]

Department of Emergency Medicine, School of Medicine, Inonu University, Malatya, Turkey
[1]Department of General Surgery, [2]Department of Radiology, [3]Department of Statistics; Firat University, Elazığ, Turkey

NO Difference in Pain score

Non of them mask underlying surgical pathology

Cochrane Review

- Tramadol for OA: No benefit for pain or function, increase adverse events.
- Tramadol for Fibromyalgia: insufficient evidence to support or refute its use
- Tramadol for Neuropathic pain: very very low quality of evidence

Drug Interactions

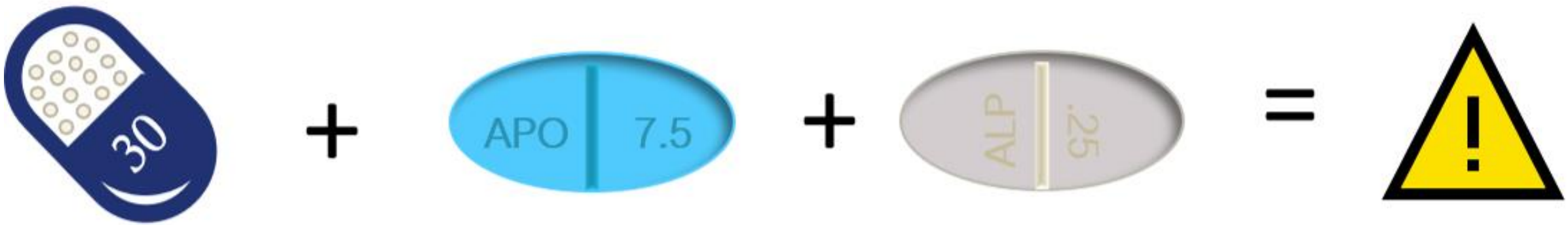


Table 3

CYP2D6 inhibitors

	Weak inhibitors	Moderate inhibitors	Strong inhibitors
Antidepressants		Sertraline	Fluoxetine
	—	Duloxetine	Paroxetine
	—	Bupropion	—
Antipsychotics	Asenapine	—	Thioridazine
		—	Perphenazine
Miscellaneous	Diphenhydramine	Terbinafine	Quinidine
	Amiodarone	—	Chloroquine
	—	—	Cinacalcet
	—	—	Imatinib

Source: References 2-5

TARGET VALUES
GLUCOSE
LEVEL
LOW
HIGH

OPEN

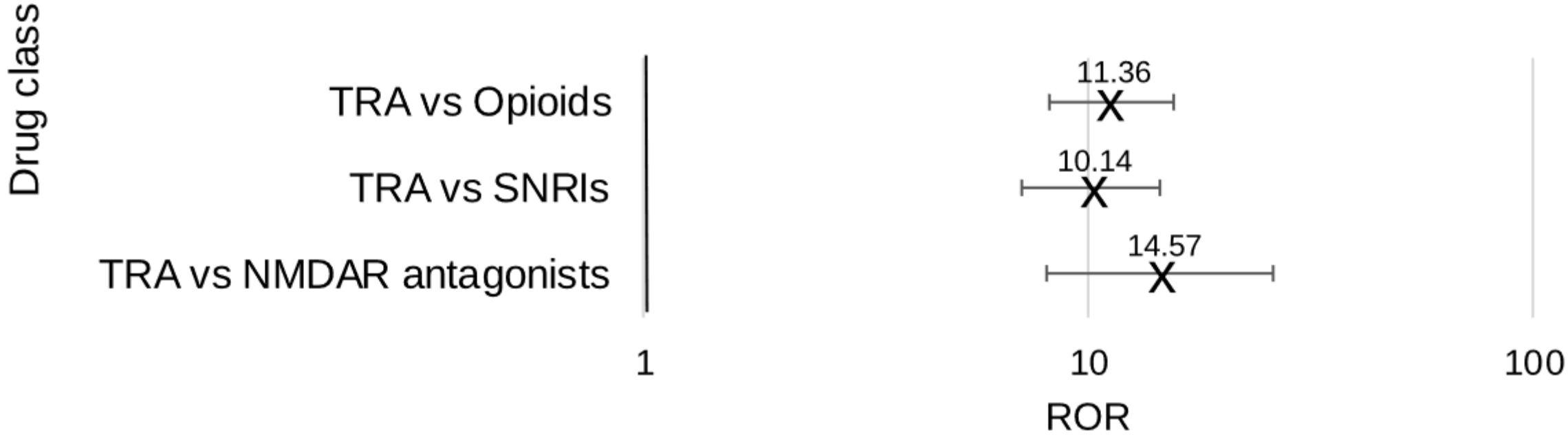
Retrospective analysis reveals significant association of hypoglycemia with tramadol and methadone in contrast to other opioids

Received: 2 July 2019
Accepted: 14 August 2019
Published online: 28 August 2019

Tigran Makunts[1], Andrew U[1], Rabia S. Atayee[1,2] & Ruben Abagyan[1]

b

Reporting odds ratios of hypoglycemia reports in **tramadol** (TRA) monotherapy cohort when compared to opioid, SNRI, and NMDAR antagonist monotherapy



Golightly *et al. Journal of Diabetes & Metabolic Disorders* (2017) 16:30
DOI 10.1186/s40200-017-0311-9

Journal of Diabetes & Metabolic Disorders

RESEARCH ARTICLE Open Access

Hypoglycemic effects of tramadol analgesia in hospitalized patients: a case-control study

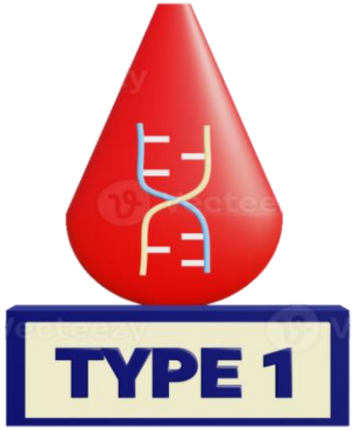
Larry K. Golightly[1,2,3*], Bonita A. Simendinger[1,2,3], Gerard R. Barber[1,2], Nancy M. Stolpman[1,2], Steven D. Kick[1,4] and Michael T. McDermott[1,2,5]

2 years observation,
≥ 1 dose of tramadol
BG measured ≥ 2 occasions within five days after the initial administration of tramadol.

2927 PT

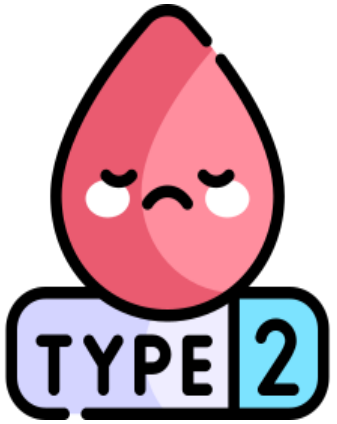
BG <70

47



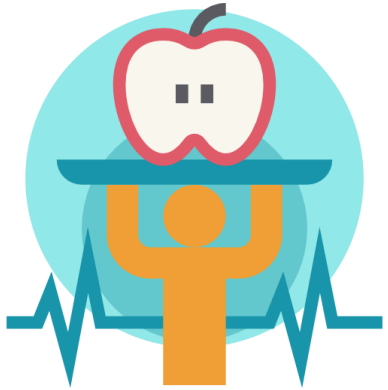
22 (47%)

673



113 (16.8%)

2207



103 (4.7%)

Pain Physician 2016; 19:E1215-E1220 • ISSN 2150-1149

Case Report

What's Tramadol Got to Do with It? A Case Report of Rebound Hypoglycemia, a Reappraisal and Review of Potential Mechanisms

Charles A. Odonkor, MD[1], and Akhil Chhatre, MD[1,2]

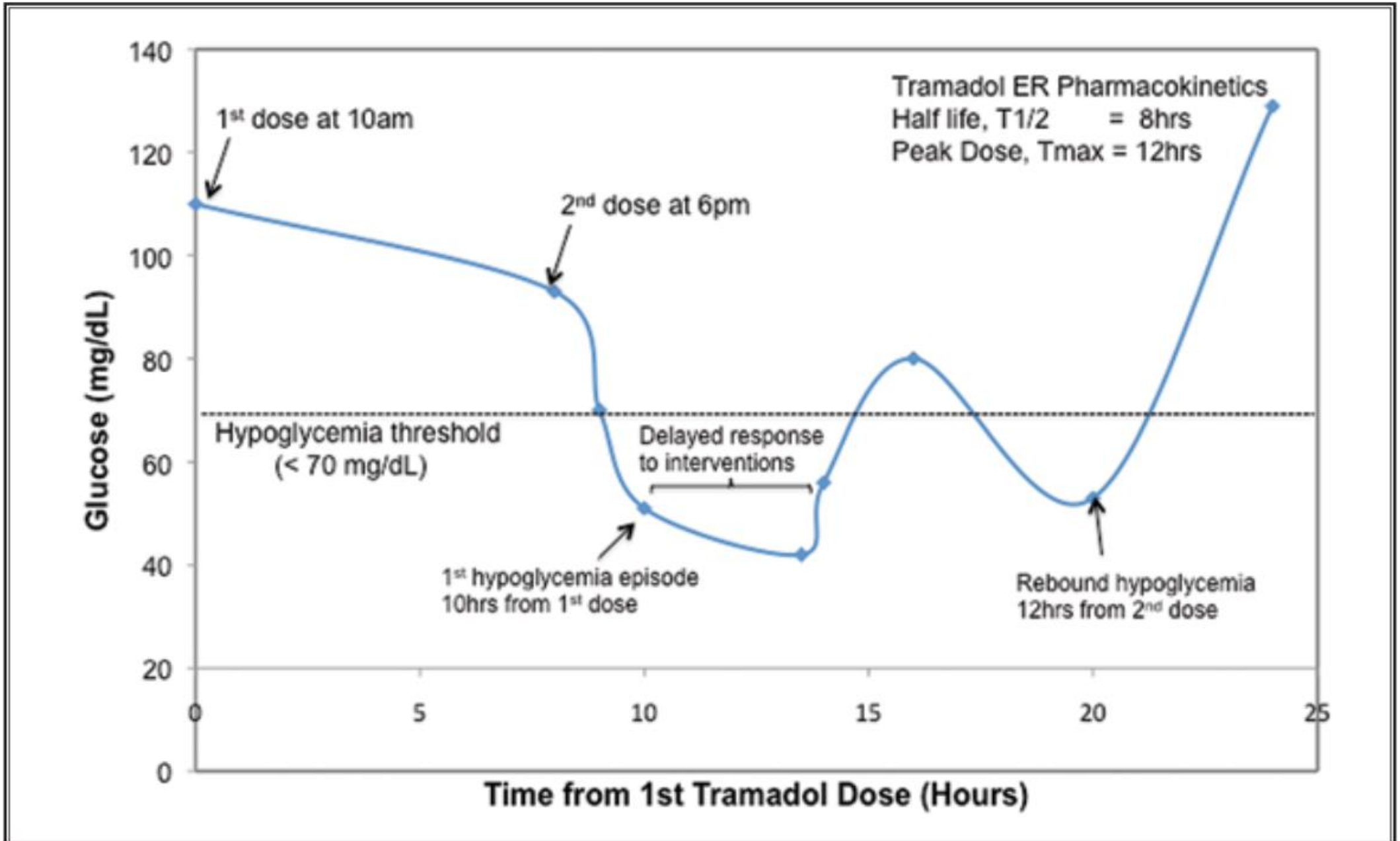
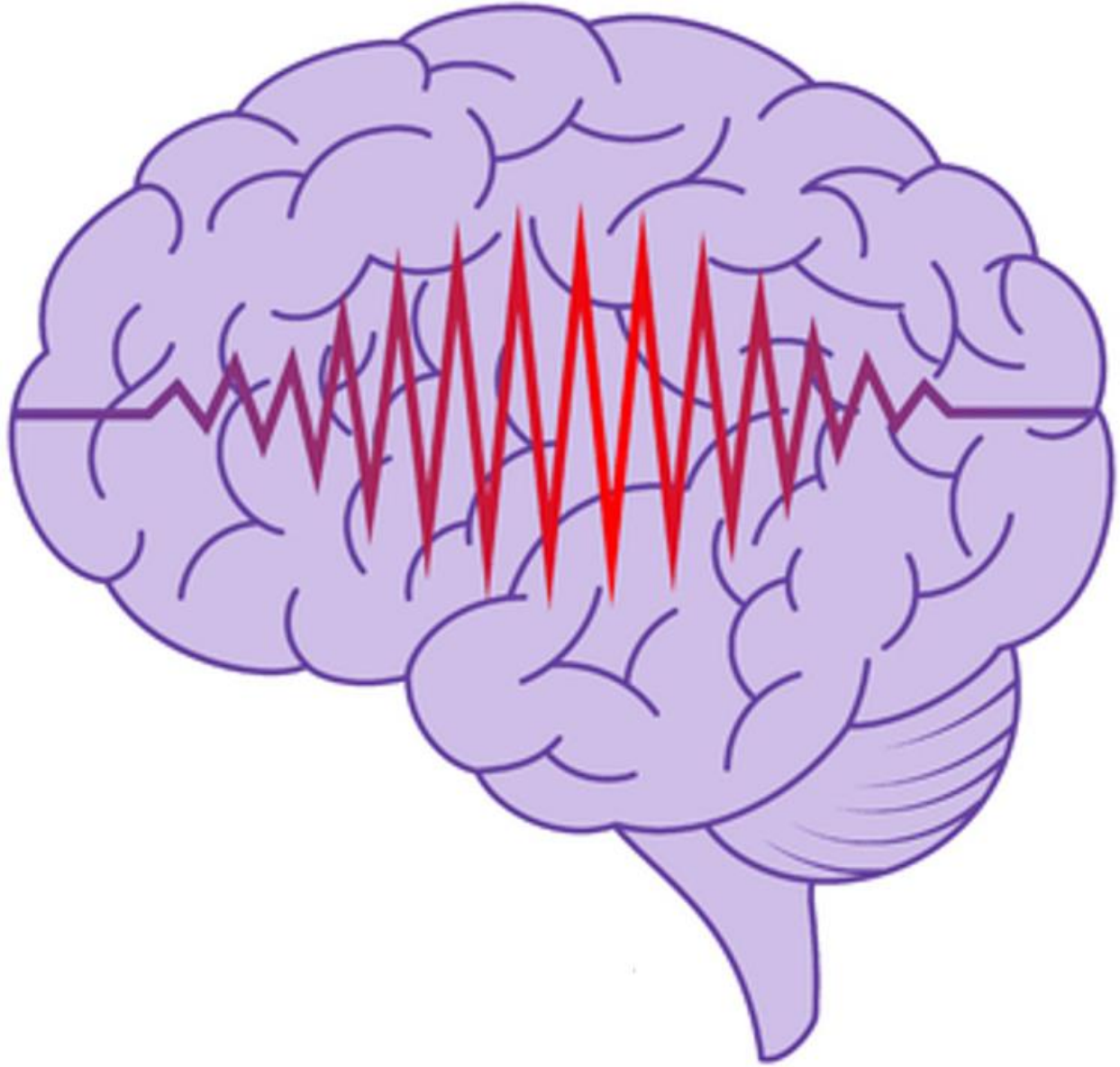


Fig. 1. *Time course of tramadol-induced hypoglycemia in a patient with type-1 diabetes mellitus.*



Tramadol and new-onset seizures

Angelo Labate,* Mark R Newton,† Graeme M Vernon,‡ Samuel F Berkovic§

* Research Fellow, Brain Research Institute,
† Neurologist, § Director, Epilepsy Research Centre,
‡ Drug Information Pharmacist, Austin Health,
Heidelberg West, VIC 3081.
s.berkovic@unimelb.edu.au

Details of eight patients with tramadol-related seizures at the First Seizure Clinic, Austin Health, April 2003–April 2004

Patient	1	2	3	4	5	6	7	8
Age (years)	18	35	31	33	48	51	25	45
Sex	M	F	F	M	M	M	F	F
Tramadol dosage (mg/day)	750	600	100	300	100	50	100	300
Treatment duration (days)	1	2	7	365	21	90	2	180
Concomitant psychotropic drug taken	No	No	No	Yes*	Yes†	No	No	No
Duration of follow-up (months)	12	9	14	9	9	3	3	2

*Chlorpromazine hydrochloride 200 mg/day. † Haloperidol 1 mg/day.

Serotonin Syndrome

Table 1 Literature results of searches for serotonin syndrome and opioid analgesics from 1974 to 2015

Opioid analgesic	Co-administered drug	Type of manuscript	Year of publication
Tramadol	Sertraline	Case report	1997
Tramadol	Fluoxetine	Case report	1999
Tramadol	Serotonin syndrome	Brief report	1999
Tramadol	Citalopram	Case report	2004
Tramadol	Overdose	Case report	2004
Tramadol	Serotonin syndrome	Review article	2005
Tramadol	Serotonin syndrome	Review article	2005
Tramadol	Serotonin syndrome	Review article	2009
Tramadol	Overdose	Case report	2010
Tramadol	Citalopram	Case report	2011
Tramadol	Accidental ingestion by infant	Case report	2011
Tramadol	SSRIs	Case report	2012
Tramadol	Chlordiazepoxide (for preventive effect on tramadol overdose induced serotonin syndrome)	Clinical trial	2013
Tramadol	Ziprasidone	Case report	2014
Tramadol	SSRIs	Case report	2014
Tramadol	Trazodone, oxycodone, bupropion	Case report	2014
Tramadol	Serotonin syndrome	Review article	2015
Meperidine	Moclobamide	Case report	1995
Meperidine	Sibutramine	Case report	2001
Meperidine	Venlafaxine, amitriptyline	Case report	2002
Meperidine	Fluoxetine	Case report	2003
Meperidine	Citalopram	Case report	2007
Meperidine	Linezolid	Case report	2008
Meperidine	Clomipramine	Case report	2015
Oxycodone	Fluvoxamine	Case report	2006
Oxycodone	Citalopram	Case report	2012
Oxycodone	Pregabalin	Case report	2013
Codeine	Sertraline	Case report	1997
Fentanyl	Sibutramine	Case report	2001
Fentanyl	Citalopram	Case report	2007
Fentanyl	Paroxetine	Case report	2008
Methadone	SSRIs	Case report	2006
Methadone	Overdose	Case report	2008
Methadone	Venlafaxine, ciprofloxacin	Case report	2009
Methadone	Duloxetine	Case report	2012
Methadone	Fentanyl	Case report	2015
Methadone	Fentanyl	Case report	2015
Morphine	Phenelzine	Case report	2015

Withdrawal

Addiction

Death

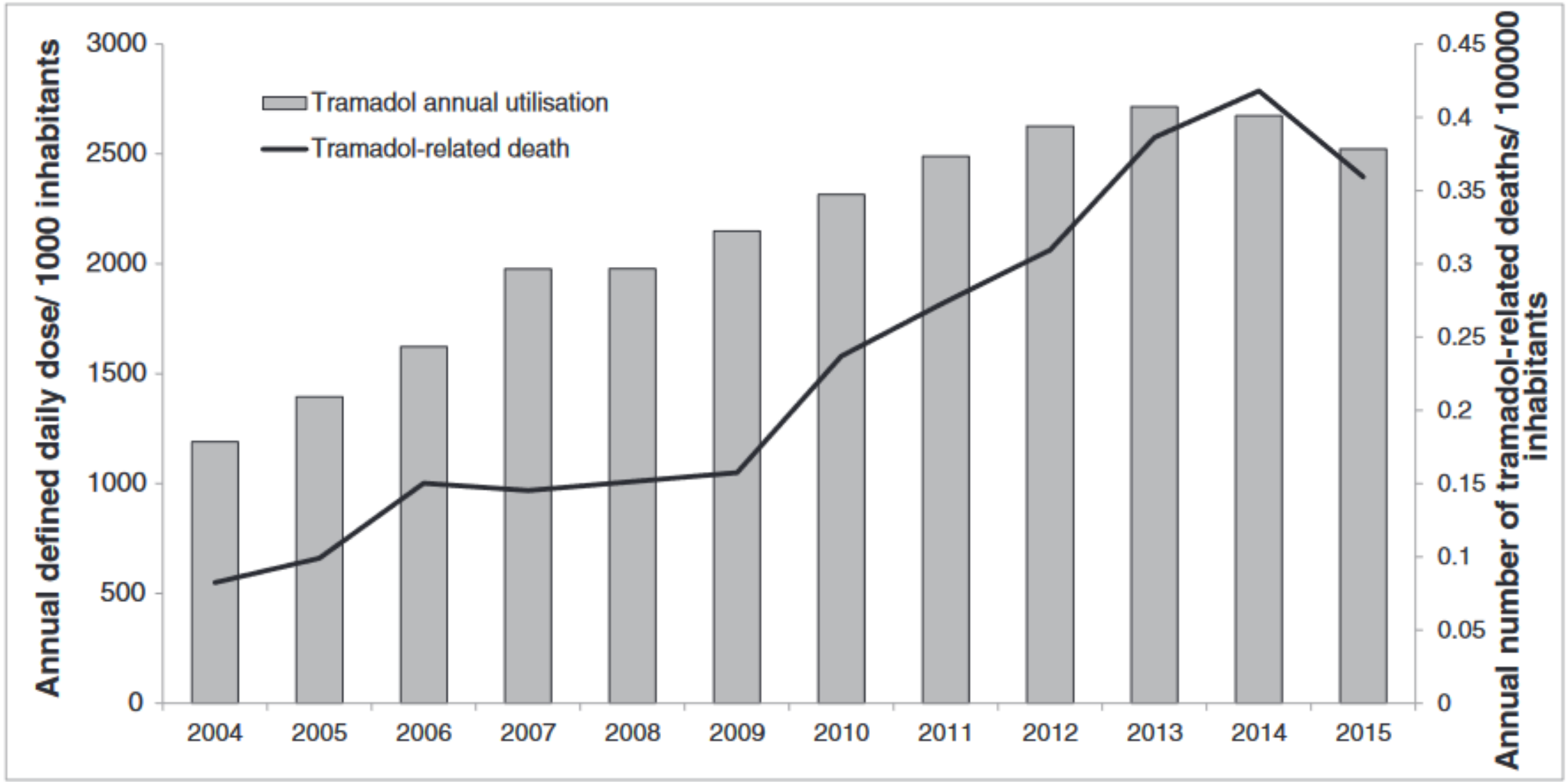
DOI: 10.1002/pds.4320

WILEY

ORIGINAL REPORT

A 15-year overview of increasing tramadol utilisation and associated mortality and the impact of tramadol classification in the United Kingdom

Teng-Chou Chen[1] | Li-Chia Chen[2] | Roger David Knaggs[1,3]



Annual tramadol utilisation and the number of tramadol-related deaths in England and Wales from 2004 to 2015

David Juurlink
@DavidJuurlink

Just told 200 medical students tramadol is the Donald Trump of pain medicines: dangerous, irrational, and you're going to regret it

When Tramadol is Appropriate